

REMARKS

Claims 2-11, 13-15 are pending. Claim 12 has been cancelled. Claim 15 is newly added. Support for newly added claim 15 is found on page 8 and page 9. An appendix with the pending claims is attached for the Examiner's convenience.

The Invention:

The present invention is directed to methods of making modified nucleosides. The methods comprise reacting an anhydro-nucleoside with a primary amine on an electron transfer moiety with a primary amine in the presence of an activation agent. The electron transfer moieties may be attached to either the 2' or 3' position of the ribose.

The choice of which anhydro-nucleoside to use depends on where the electron transfer moiety is to be attached. If the electron transfer moiety is to be attached to the 2' position of the ribose of a pyrimidine nucleoside, a 2,2' anhydro-nucleoside is used. For attachment to the 3' position of the ribose of a pyrimidine nucleoside, a 2,3' anhydro-nucleoside is used. Similarly, anhydro-nucleosides also can be made by forming a bridge between the N-3 of the purine and the 2', 3' or 5' position on the ribose.

Rejections Under 35 U.S.C. § 112, second paragraph

Claims 2-14 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Specifically, the Examiner states that without chemical formulas to define what the functional language is intended to define, the applicant is unlikely to meet the requirements of the statute.

Applicants respectfully point out when the subject matter of the invention relates to a process, a claim need only recite the necessary steps. There is no requirement that a structure be disclosed in a method claim. *Dennison Mfg. Co. v. Ben Clements & Sons, Inc.*, 467 F. Supp. 391, 203 USPQ 895 (1979, SD NY). An example of a method patent in which only the necessary steps for making a class of chemical compounds is U.S. Patent No. 6,043,061.

Rejection of Claim 7 under 35 U.S.C. § 112, second paragraph

Specifically, Claim 7 is rejected for using the term “comprising”. The Examiner states it is incorrect to use the word comprising when claiming a chemical structure. The Examiner’s position appears to be that compounds cannot “comprise” additional components. The Applicants respectfully disagree.

Comprising is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim. In *Genetech, Inc. v. Chiron Corp.*, 112 F.3d 495 (Fed. Cir. 1997). The use of “comprising” is not restricted based on the nature of the material being claimed, rather it is the prior art that determines whether an open ended term such as “comprising” is appropriate.

Thus, in *Ex parte Sawyer* (1961, Bd App) 130 USPQ 476, where an Examiner had rejected a claim because of the use of “comprising”, the Board held:

There is no prior art which necessitates restriction of the claims. The examiner also felt the term consisting essentially of should be used. We see no need in the absence of pertinent art why the claims should be so restricted as it is obvious that a wide variety of materials may be thickened with the claimed composition and various inert materials may be added to the composition without destroying the same or materially affecting its function.

Similarly, In *In re Baxter*, 210 U.S.P.Q. 795, 802-803 (C.C.P.A. 1981), the court in interpreting the following claim “A process which comprises interpolymerizing monomers comprising ethylene and propylene in the presence of . . .” stated:

In the absence of ambiguity, it is fundamental that the language of a count should be given the broadest reasonable interpretation it will support and should not be given a contrived, artificial, or narrow interpretation which fails to apply the language of the count in its most obvious sense. . . . Bearing in mind the above considerations and recognizing that Baxter’s proposed count A is a comprising-type count, we are satisfied that the scope of the proposed count includes polymerizing propylene with any other monomer (copolymerization), such as ethylene, as well as homopolymerization. As long as one of the monomers in the reaction is propylene, any other monomer may be present, because the term “comprises” permits the *inclusion* of other steps, elements, or materials.

Applicants submit that the present specification supports the use of use of “comprising” because compounds which may serve as electron transfer moieties are defined on pages 7-8; compounds which contain primary amines are defined on page 6, and methods for making a 2' modified nucleoside comprising an electron transfer moiety and a primary amine are disclosed on pages 18-20, Example 1, and Figures 2 and 3. Furthermore, the Examiner has provided no prior art which warrants a narrowing of the claim language.

Accordingly, applicants submit that it is not incorrect to use the term “comprising” in this context and respectfully request withdrawal of the rejection of Claim 7 under 35 U.S.C. § 112, second paragraph.

In addition, Claim 7 is rejected for using generic terms with many possible structural meanings and for using terms which are meaningless unless the details of the chemical reaction are provided. Specifically, the Examiner rejects the use of “anhydronucleoside”, “electron transport moiety”, “activated anhydronucleoside”, “cyclization agent” and “cyclized intermediate”.

To reiterate section 2173.05(a) of the M.P.E.P., “the meaning of every term used in a claim should be apparent from the prior art or from the specification and drawings at the time the application is filed”. As argued previously, terms such as “anhydro-nucleoside” and “nucleoside analog” are art recognized terms. For example, one of the references provided by the Examiner, Nexstar '102, refers to cyclization reactions (see page 3, line 29 through page 4, line 3); analogs of nucleosides (see page 1, lines 25 and 27); and anydronucleosides (see page 21). Other references, such as Sebesta, et al., *Tetrahedron*, (1996) 46:14385-14402, cited by the Examiner, use the terms nucleoside analogs and anhydronucleosides without further definition. See for example, the title, last sentence of the abstract, first sentence of the introduction, first sentence of the background, and throughout the entire paper.

In addition, the Applicant has defined what is meant by each of these terms in the application and drawings. According to M.P.E.P. § 2173.05(a), “when the specification states the meaning that a term in the claim is intended to have, the claim is examined using that meaning.”

The general definition of electron transfer moiety is found at page 7, lines 13-25 of the specification:

By the terms “electron donor moiety”, “electron acceptor moiety”, and “electron transfer moieties” or grammatical equivalents herein refers to molecules capable of electron transfer under certain conditions.

Beginning on page 7, line 24 through page 11, line 9, descriptions of preferred electron transport moieties are found.

Definitions for “anydronucleoside” and “activated anydronucleoside” also are provided in the specification. For example, “anydronucleoside” is defined as a “2,2'-, 2,3'- or 2,5' anydronucleoside, comprising an oxygen bridge between the C-2 of the base pyrimidine and the C-2' or C-3' of the ribose or ribose analog.” See specification at page 18, line 23 through page 19, line 13. An “activated anydronucleoside” is formed when an anydronucleoside and a signalling moiety comprising a primary amine are added together in the presence of an activation agent. See page 20, lines 1-2. On page 20, lines 10-11, an “activated anydronucleoside” is defined as an “anydronucleoside ready to react with the signalling moiety comprising a primary amine to form a carbamate.”

The Examiner states that the terms “cyclization agent” and “cyclized intermediate” are meaningless because the details of the chemical reaction are not provided. Applicants wish to draw the Examiner’s attention to Figures 1 and 2. In Figure 1 a generalized scheme for making modified nucleosides is illustrated. In Figure 2, specific details of the reaction are included. Specifically, reaction e) demonstrates the formation of a cyclized intermediate in the presence of a cyclization agent.

Accordingly, applicants submit the terms “anydronucleoside”, “electron transport moiety”, “activated anydronucleoside”, “cyclization agent” and “cyclized intermediate”

are either art defined terms or are defined in the specification. Applicants request withdrawal of the rejection.

Rejection of Claim 3 under 35 U.S.C. § 112, second paragraph

The Examiner states claim 3 is indefinite for failing to specify the chemical structural variables which define the phosphoramidite modified nucleoside. Applicants submit that the amendment made to Claim 2 in the previous office action clarifies that the phosphoramidite moiety is added to the 3' position of the nucleoside. In addition, applicants draw the Examiner's attention to Figure 3, reaction h), which illustrates a phosphoramidite-derivatized nucleoside as disclosed in Claim 3.

As argued previously, the specification on page 21, lines 15-22 makes it clear that the phosphoramidite modified nucleotide that results is known in the art. In *In re Sneed*, the court held "claims in an application are to be given their broadest reasonable interpretation consistent with specification, and that claim language should be read in light of the specification as it would be interpreted by one of ordinary skill in the art." *In re Sneed*, 710 F.2d 1544,1548 (1983). As the Examiner notes, the specification makes reference to the Caruthers process of nucleic acid synthesis. See specification page 21, lines 21-22. Thus, the phosphoramidite modified nucleoside referred to is known to one of ordinary skill in the art and does not require further elucidation. Accordingly, the rejection should be withdrawn.

Rejection of Claim 5 under 35 U.S.C. § 112, second paragraph and 35 C.F.R. § 1.75(c)

Claim 5 is rejected for the use of the term "nucleoside analog". Applicants submit that "nucleoside analog" is an art recognized term as evidenced by the numerous references describing nucleic acid analogs which have been incorporated by reference and are listed in the specification at page 4, line 2 through page 5, line 4. Accordingly, applicants submit the specification combined with the prior art provides sufficient guidance to permit the ordinary practitioner to determine which compounds qualify as a "nucleoside analog". Applicants respectfully request withdrawal of the rejection.

The Examiner objects to claim 5 as being of improper dependent form under 35 C.F.R. § 1.75(c). Applicants have amended claim 5 to include the language “further comprises”. Applicants thank the Examiner for his suggestion. Applicants request withdrawal of the rejection.

Rejection of Claim 6 under 35 U.S.C. § 112, second paragraph

Claim 6 has been amended to correct the spelling of the term “carbonyldimidazole” to its proper spelling “carbonyldiimidazole”. Accordingly, the rejection should be withdrawn.

Rejection of Claim 8 under 35 U.S.C. § 112, second paragraph

Claim 8 has been amended to clarify that the electron transfer moiety is a transition metal complex comprising a transition metal chelated by at least one ligand. As outlined in the specification on page 8, line 11 through page 11, line 8, any number of ligands may be used including sigma donors and organometallic ligands. Accordingly, the rejection should be withdrawn.

Rejection of Claim 9 under 35 U.S.C. § 112, second paragraph

Claim 9 has been amended to clarify which transition metals are included in the transition metal complexes. Accordingly, applicants request withdrawal of the rejection.

Rejection of Claim 10 under 35 U.S.C. § 112, second paragraph

Claim 10 has been amended to make it consistent with the terms in dependent claims 13 and 14 and provide proper antecedent basis for the terms in claims 13 and 14. Accordingly, the rejection should be withdrawn.

Rejection of Claim 11 under 35 U.S.C. § 112, second paragraph

Claim 11 has been amended to clarify that the ligand is a sigma donor as defined in the specification at pages 8-9. Accordingly, the rejection should be withdrawn.

Rejection of Claim 12 under 35 U.S.C. § 112, second paragraph

Claim 12 has been cancelled. Thus, the rejection is moot.

Rejection Under 35 U.S.C. § 112, first paragraph

Claims 2-14 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which lacks adequate enabling support.

The remarks set forth above also pertain to this rejection. Applicants, therefore, respectfully request withdrawal of the rejection.

Rejection Under 35 U.S.C. § 103(a)

Claims 10-12 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Nexstar.

The Examiner states that claim 14 of the Nexstar reference discloses 2'-substituents which contain 7 and 3 oxygens, thereby having the potential to act as ligands. Applicants respectfully disagree.

The Nexstar reference teaches a method for making modified nucleosides. However, the Nexstar reference does not teach the synthesis of nucleosides modified at the 2' position with a transition metal complex.

When rejecting claims under 35 U.S.C. § 103, the Examiner bears the burden of establishing a *prima facie* case of obviousness. *See, e.g., In re Bell*, 26 USPQ2d 1529 (Fed. Cir. 1993); M.P.E.P. § 2142. To establish a *prima facie* case, three basic criteria must be met: (1) the prior art must provide one of ordinary skill with a suggestion or motivation to modify or combine the teachings of the references relied upon by the Examiner to arrive at the claimed invention; (2) the prior art must provide one of ordinary skill with a reasonable expectation of success; and (3) the prior art, either alone or in combination, must teach or suggest each and every limitation of the rejected claims. The teaching or suggestion to make the claimed invention, as well as the reasonable expectation of success, must come from the prior art, not Applicant's disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991); M.P.E.P. § 706.02(j). If any one of these criteria is not met, *prima facie* obviousness is not established.

Claims 10-12 are not obvious over Nexstar

As amended, Claim 10 is directed to a method of making a 2' modified nucleoside with a covalently attached transition metal complex comprising a polydentate ligand and a transition metal.

As amended, Claim 11 is directed to a method of making a 2' modified nucleoside where the coordination atom is a sigma donor ligand attached to a transition metal.

Claim 12 has been cancelled and the rejection is moot.

As the use of ligands to chelate metal atoms is not disclosed in Nexstar, applicants respectfully submit that the Examiner has failed to make out a *prima facie* case of obviousness against Claims 10-11. Applicants request that the rejection be withdrawn.

Claims 2-7 are not obvious over Nexstar

Claims 2-7 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Nexstar.

Claim 7 is directed to methods of making nucleosides modified with electron transfer moieties. Preferably, the electron transfer moiety comprises a transition metal coordinately bond to one or ligands. See for example the specification at pages 7-11. Further, a primary amine must be an integral part of the electron transfer moiety prior to its additon to the nucleoside. See specification at page 6, lines 8-14.

As argued previously, the Nexstar reference teaches a method for making modified nucleosides that does not include coordinate-covalently bonded metal atoms or ions.

Claims 2-6 depend from Claim 7 and necessarily contain each and every element of Claim 7. Therefore, the Examiner has also failed to establish a *prima facie* case of obviousness against Claims 2-6 for the same reasons he failed to do so for Claim 7. Accordingly, Applicants respectfully request the withdrawal of the rejection of Claims 2-7 under 35 U.S.C. § 103(a) as being obvious over Nexstar as a *prima facie* case of obviousness has not been made.

Applicants submit the claims are now in condition for allowance and an early notification of such is respectfully solicited. If after review, the Examiner feels there are

further unresolved issues, the Examiner is invited to call the undersigned at
(415) 781-1989.

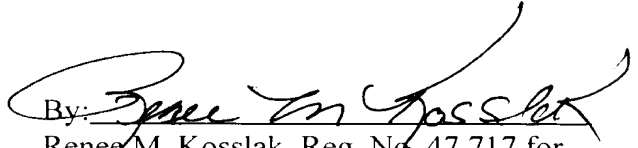
Attached hereto is a marked up version of the changes made to the specification
and claims by the current amendment. The attached page is captioned **"Version with
markings to show changes made."**

The Commissioner is authorized to charge any additional fees, including any
extension fees, which may be required, or credit any overpayment to Deposit Account
No. 06-1300 (Our Order No. A-67412/RFT/RMS).

Dated: 4/19/01

Respectfully submitted,

FLEHR HOHBACH TEST
ALBRITTON & HERBERT LLP

By: 
Renee M. Kosslak, Reg. No. 47,717 for
Robin M. Silva, Reg. No. 38,304

Four Embarcadero Center - Suite 3400
San Francisco, California 94111-4187
Telephone: (415) 781-1989
1031459.RMK

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

Claim 5 has been amended as follows:

5. (Twice Amended) A method according to claim 7 wherein said nucleoside further comprises a nucleoside analog.

Claim 6 has been amended as follows:

6. (Twice Amended) A method according to claim 7 wherein said activating agent is [carbonyldimidazole.]carbonyldiimidazole.

Claim 7 has been amended as follows:

7. A method for making a 2' modified nucleoside comprising a covalently attached electron transport moiety, said method comprising:

- a) adding an anhydro-nucleoside and a electron transfer moiety comprising a primary amine in the presence of an activation agent to form an activated anhydro-nucleoside;
- b) treating said anydronucleoside with a cyclization agent to form a cyclized intermediate; and
- c) treating said cyclized intermediate with a base to form said 2' modified nucleoside.

Claim 8 has been amended as follows:

8. (Amended) A method according to claim 7 wherein said electron transfer [moieties]moiety [are]is a transition metal complex[es] comprising a transition metal and at least one ligand.

Claim 9 has been amended as follows:

9. (Amended) A method according to claim 8 wherein said [electron transfer moieties] transition metal complex [are] comprises a transition metal selected from the group consisting of ruthenium, rhenium, osmium, [platinum]platinum, cobalt, and iron.

Claim 10 has been amended as follows:

10. (Amended) A method for making a 2' modified nucleoside comprising a covalently attached [polydentate ligand]transition metal complex, said method comprising:

- a) adding an anhydro-nucleoside and a polydentate ligand comprising a primary amine in the presence of an activation agent to form an activated anhydro-nucleoside;
- b) treating said anydronucleoside with a cyclization agent to form a cyclized intermediate; [and]
- c) treating said cyclized intermediate with a base to form said 2' modified nucleoside[.]; and
- d) adding a transition metal.

Claim 11 has been amended as follows:

11. (Amended) A method according to claim [10]8 wherein the coordination atom of said [polydentate] ligand is selected from the group consisting of nitrogen, oxygen, sulfur, carbon and phosphorus.

Claim 12 has been cancelled.

Claim 13 has been amended as follows:

13. (Amended) A method according to claim [12]10 wherein said organometallic ligand is ferrocene.

Claim 14 has been amended as follows:

14. (Amended) A method according to claim [12]10 wherein said organometallic ligand is a metallocene.